

Remarks**Claims**35 USC § 102(b) Rejection of Claims 1 - 3 and 10

The Office Action rejected Claims 1 - 3 and 10 under 35 USC 102(b) as being anticipated separately by Hamada *et al.*, Tsukuda *et al.*, or Li *et al.*

Applicants have canceled independent Claim 1 and added New Claim 11, which includes the features of Claims 1 and 8. Claim 8, which was dependent from Claim 1, was not found to be anticipated by Hamada *et al.*, Tsukuda *et al.*, or Li *et al.* Therefore New Claim 11 is not anticipated by Hamada *et al.*, Tsukuda *et al.*, or Li *et al.* Additionally, since Claims 2 and 3 are now dependent from Claim 11, they also are not anticipated by Hamada *et al.*, Tsukuda *et al.*, or Li *et al.*

The Examiner is requested to withdraw Hamada *et al.*, Tsukuda *et al.*, and Li *et al.* as 102(b) references. In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claims 2, 3 and 11.

35 USC § 103(a) Rejection of Claims 1 and 8

The Office Action rejected Claims 1 and 8 under 35 USC 103(a) as being unpatentable over Tsukuda *et al.* in view of Molnar-Kimber *et al.* The Office Action stated that Tsukuda disclosed adenovirus and A549 cells, and that Molnar-Kimber disclosed tumor cells for tumor vaccination. The Office Action (page 12, line 2 from the bottom) alleges that Tsukuda teaches the use of A549 cells infected with adenovirus for treatment of tumors, and Molnar-Kimber teaches that irradiated tumor cells infected with an oncolytic virus can induce an immune response in the patient by forming complexes with tumor cells. The Examiner stated, based on the disclosure of these references, that improving anti-tumor effects by inducing a tumor immune response in carrier cells is obvious for a person skilled in the art.

Applicants disagree with the conclusion of the Office Action and Traverse.

Although Tsukuda describes A549 cells, such cells are only used for producing tumor model animals. It is alleged that Tsukuda uses A549 cells infected with adenovirus for tumor treatment. However, Tsukuda only teaches the treatment of tumors by injecting the specific

adenovirus directly into the tumor produced with A549 cells. Tsukuda is silent about the treatment of tumors using A549 cells infected by an oncolytic virus.

Further, Molnar-Kimber discloses producer cells that correspond to carrier cells, and also teaches that it is important to infect the carrier cells with a virus (page 12, lines 5 to 6 of WO99/45783). Molnar-Kimber exemplifies PA-1 cells, REN cells, PER cells, C6 cells, and 293 cells as producer cells; however, A549 cells are not mentioned.

Additionally, it is alleged that Molnar-Kimber teaches the use of irradiated tumor cells for inducing a tumor immune response. Although Molnar-Kimber describes the irradiation of tumor cells for preventing replication inside the patient's body (page 12, lines 26 to 27, and page 13, lines 5 to 8), Molnar-Kimber is silent about the administration of tumor cells for inducing tumor vaccination in the patient's body prior to the administration of A549 cells infected with an oncolytic virus.

Both of the references are silent about the important components of the present invention, such as, tumor cells for tumor vaccination and A549 cells infected with an oncolytic virus. Accordingly, these references would not make it obvious to try the features of Claim 11 and would not lead a person skilled in the arts to conceive of the present disclosed kit.

Further, applicants show that the presently disclosed kit can achieve unpredictable results compared to the disclosures of the references cited in the Office Action. Specifically, none of the references teach or suggest a significantly high anti-tumor effect achieved by using the components of the presently disclosed kit.

The Office Action alleges that Molnar-Kimber teaches the induction of a tumor immune response in patients by using irradiated tumor cells as producer cells. However, as is clear from Fig. 22 and paragraph [0120] of the present application, a remarkable anti-tumor effect was achieved in the animals subjected to the tumor immune treatment prior to the injection of carrier cells infected with an oncolytic virus, compared to the animals treated with only carrier cells. Additionally, the tumors disappeared, and no recurrences were observed in all the model animals subjected to the treatment according to the present disclosure.

Furthermore, as is clear from Figure 1 of the present application, when oncolytic adenovirus was infected using A549 cell as the carrier cell, the A549 cell exhibited a proliferation inhibitory effect about 100-fold greater, in terms of the cell numbers at IC50, than that in PA-1 cell (paragraph [0025] and Figure 1).

Additionally, as is clear from Figure 6 of the present application, complete regression of the tumor in a nude mouse model was observed only when A549, 293, SW626, and HT-3 cells were used as the carrier cell. Complete tumor regression was not observed when other cells were used as the carrier cell.

Also, all tumors completely disappeared when an A549 cell was used as the carrier cell and no reoccurrence was observed (paragraph [0027] of the present application)

The Examples disclosed in the application confirm a remarkably superior effect was obtained when an A549 cell was used as the carrier cell both *in vitro* and *in vivo*, compared to when a PA-1 cell was used as the carrier cell.

The applicants prepared survival curves (employing the Kaplan-Meier method) when A549, 293, SW626, HT-3, PA-1, MH and C33A cells were used as the carrier cell, in accordance with the method disclosed in paragraphs [0112] to [0116] (Example 6) in the application. Figure A (Appendix I) shows this experiment.

As shown in Figure A, only when A549 or 293 cells were used as the carrier cell was a survival rate of 100% exhibited. In contrast, when SW626 or HT-3 cells were used as the carrier cell, the survival rates were approximately 60% (SW626 cells) and 40% (HT-3 cells). When PA-1, MH, or C33A cells were used as the carrier cell, no anti-tumor effects were observed in terms of the survival curve.

It is clearly demonstrated that an excellent anti-tumor effect only can be achieved when A549 cells (or 293 cells) are used as the carrier cell.

In “Coukos *et al.*, Clinical Cancer Research, 5, 1523-1537, 1999” (Appendix II), the anti-tumor effect was examined by infecting PA-1 cells with HSV virus. As is clear from the results shown in Figure 7 of Coukos *et al.*, a reoccurrence was observed of all tumors even though there was a slight increase in the survival rate. Therefore, it is clear that PA-1 cells cannot obtain a complete tumor regression effect. There was no significant difference in the results when PA-1 cells were used as the carrier cell, and when the virus was administered without using a carrier (corresponding to HSV1716 in the Figure 7).

Coukos *et al.* appears to correspond to Molnar-Kimber *et al.* cited in the current Office Action. Furthermore, this document was also disclosed in paragraphs [0003] to [0006] of the present application.

Figure 5 in Wei, *et al.*, 2007 (Appendix III) shows there is no significant difference in the survival rate between BOEC (blood outgrowth endothelial cells used as the carrier cells) and MV-Edm (measles virus only)

Figures 6A and 6B in “Hakkarainen, T., *et al.*, Human Gene Therapy, 18: 627-641, 2007” (Appendix IV) show that when oncolytic adenovirus was infected using mesenchymal stem cells as the carrier cells, the anti-tumor effect achieved was as low as approximately 10% survival rate.

As shown above, the disclosed cancer gene therapeutic drug kit as presently claimed can only achieve the remarkably excellent anti-tumor effect when A549 cells are used as the carrier cell and it is clear that a satisfactory anti-tumor effect cannot be obtained when cells other than A549 cells are used as the carrier cell.

None of the cited references would make it obvious for a person skilled in the art to try using A549 cells as the carrier cell, and the references are silent about the unexpected excellent effects achieved by the use of A549 cells. A skilled artisan would not have been able to select a cell line that achieves remarkable anti-tumor effects among various cells that are usable as the carrier cell, and use such a cell line in treating cancer, in combination with the administration of tumor cells to induce tumor vaccination, based on the disclosures of the cited references.

The Examiner is requested to remove the combination of Tsukuda *et al.* in view of Molnar-Kimber *et al.* as 103(a) references. In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claim 11.

Rejoinder of Claims 4 - 7 and 9

Claims 4 – 7 and 9 are currently withdrawn. As Claim 11 is allowable, as amended, and Claims 4 – 7 contain all the features of the claim from which they depend, the Examiner is respectfully requested to rejoin Claims 4 - 7. In light of the foregoing arguments, the Examiner is respectfully requested to allow Claims 4 – 7 and 9.

No Disclaimers or Disavowals

Although the present communication may include alterations to the claims, the Applicants are not conceding in this application that previously pending claims are not patentable. Rather, any alterations or characterizations are being made to facilitate expeditious

prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

Claims 2 - 7, 9 and 11 are pending. Claims 2 and 3 are Currently amended. Claims 4 - 7 and 9 are Withdrawn-Currently amended. Claims 1, 8 and 10 are Canceled.

No additional fees are believed due; however, the Commissioner is authorized to charge any additional fees now and in the future which may be due, including any fees for additional extension of time, or credit overpayment to credit card information.

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